17. **(Once Amended)** A pharmaceutical composition comprising a nucleic acid encoding a sequence that is complementary to at least a portion of a Hepatitis A virus IRES which contains a YX AUG sequence, and a pharmaceutically acceptable carrier, wherein the nucleic acid is present in an amount effective for inhibiting viral replication, wherein Y is a pyrimidine tract between 4 to 12 nucleotides, and wherein X is a random spacer sequence of between 5 to 30 nucleotides.

Please add new Claim 18 as follows:

18. **(Newly Added)** A composition comprising a nucleic acid encoding a sequence that is complementary to at least a portion of a Hepatitis A virus IRES which contains a YX AUG sequence, wherein the nucleic acid is present in an amount effective for inhibiting viral replication, and wherein Y is a pyrimidine tract between 4 to 12 nucleotides, wherein X is a random spacer sequence of between 5 to 30 nucleotides.

Please cancel Claim 6 without prejudice.

REMARKS

Claims 3, 6, 8-10 and 17 are pending in the instant application. Claim 17 stands rejected under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure; and Claims 3, 6, 8-10 and 17 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

Claim 6 has been canceled herein without prejudice; Claims 3, 10, and 17 have been amended herein; and Claim 18 has been added herein. Support for amended Claim 3, and Claims 8-10 depending therefrom, can be found in the originally filed claim, and throughout the specification, and more specifically in the specification at (page:line) 104:2-107:20. Claim 10 has been amended herein to correct the dependency of this claim. Support for amended Claim 17 can be found in the originally filed claim, and throughout the specification, and more specifically in the specification at (page:line) 143:21-28. Support for new Claim 18 can be found in originally filed Claim 17, and throughout the specification, and more specifically in the specification at (page:line) 143:21-28. Thus, no new matter is added

IN THE SPECIFICATION:

Please amend the specification to delete pages 164-171.

REMARKS

In the Office Action dated September 13, 2002, Applicants are directed to delete one of two sequence listings in the specification. Responsive to these directions, Applicants amend the specification herein to delete pages 164-171 to delete one of the two sequence listings. Thus, no new matter is added by way of the amendment herein.

CONCLUSION

In view of the foregoing and the attached response filed March 13, 2002, Applicants submit that all claims now pending in the Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 781-1989.

Respectfully submitted,

FLEHR HOHBACH TEST
ALBRITTON & HERBERT LLP

Date: 3/15/02

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by way of the claim amendments and addition made herein. A "Marked-Up Version" is attached to identify the amendments to the claims.

Rejection Under 35 U.S.C. § 112, First Paragraph

Claim 17 stands rejected under 35 U.S.C. § 112, first paragraph, as lacking an enabling disclosure.

Claim 17 recites, *inter alia*, a pharmaceutical composition comprising a nucleic acid fragment complementary to at least a portion of a Hepatitis A virus IRES which contains a YXAUG sequence, and a pharmaceutically acceptable carrier, wherein the nucleic acid fragment is present in an amount effective for inhibiting viral replication.

Citing the *In re Wands* factors, the Examiner concludes that a skilled artisan would require undue experimentation to practice the invention of Claim17. The Examiner's primary concern and argument is that the skilled artisan would need to develop formulations and delivery protocols for the claimed pharmaceutical composition in order to practice the claimed invention. Applicants respectfully disagree.

Applicants have demonstrated, as the Examiner has noted, that the claimed composition effectively inhibits *in vitro* translation of viral nucleic acid in a virus containing an internal ribosomal entry site (IRES). No more is required to enable the claimed invention. The Examiner seems to require disclosure on exact formulations and delivery protocols for a method of treating an individual infected by Hepatitis A with the claimed composition. As a composition claim, Claim 17 does not recite method steps for treating an individual. Thus, the disclosure demanded by the Examiner is not required for the claimed composition.

Even if such disclosure were required, the skilled artisan at the time of the invention was capable of determining the protocols and formulations required by the Examiner. In support of this position Applicants submit herewith references 1-5 listed below, all of which were published after the filing date.

1. Zhang *et al.*, Antisense Oligonucleotide Inhibition of Hepatitis C Virus (HCV) Gene Expression in Livers of Mice Infected with an HCV-Vaccinia Virus Recombinant, *Antimicrob. Agents Chemother.* 43(2):347-353 (Feb. 1999)

2. WO 99/29350
3. WO 00/06590
4. U.S. Pat. No. 6,174,868 (issued Jan. 16, 2001)
5. U.S. Pat. No. 6,284,458 (issued Sep. 4, 2001)

Applicants submit that the above later-dated publications show that the disclosure of the present application would have been enabling at the time of filing. As taught in *In re Wilson*, 135 USPQ 442, 444 (CCPA 1962); *Ex parte Obukowicz*, 27 USPQ 2d 1063 (BPAI 1993); *Gould V. Quigg*, 3 USPQ 2d 1302, 1305 (Fed. Cir. 1987), a later dated publication can provide evidence that the disclosed device would have been operative.

In general the references demonstrate that one skilled in the art would know how to develop effective delivery protocols and formulations to treat an individual (*e.g.*, an animal model) with antisense therapy. Moreover, in each of the references the antisense molecules inhibited the translation of a Hepatitis virus nucleic acid sequence by targeting the 5' untranslated region of the viral genome. Lastly, Applicants note that in references 4 and 5, both U.S. Patents, the issued claims cover pharmaceutical compositions comprising the oligonucleotide and a pharmaceutical carrier. Applicants further note that in the case of reference 5, the issued claims are directed to pharmaceutical composition where no *in vivo* data is disclosed in the reference, in contrast to the requirements dictated by the instant rejection.

Applicants respectfully submit that the invention of Claim 17 is fully enabled by the specification. Accordingly, Applicants respectfully request withdrawal of the rejection of Claim 17 under 35 U.S.C. § 112, first paragraph.

Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 3, 6, 8-10, and 17 stand rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

Claim 3, and Claims 8-10 depending therefrom, have been amended herein to more clearly recite a method of screening; Claim 6 is canceled herein; and Claim 17 is amended herein to clearly define the symbols Y_nX_m. Applicants submit that the above amendments

and remarks both address and obviate the rejection under 35 U.S.C. § 112, second paragraph as being indefinite and, thus, withdrawal of this rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants submit that all claims now pending in the Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at (415) 781-1989.

Respectfully submitted,

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Marked-Up Version Of Pending and New Claims

3. **(Once Amended)** A method of screening for a nucleic acid capable of inhibiting translation of a nucleic acid sequence containing an IRES wherein said nucleic acid sequence is [obtained] from a Hepatitis A virus, said method comprising the step of administering to an organism [a] said nucleic acid encoding a sequence that is [fragment] complementary to at least a portion of said IRES, wherein the ability of [the] said nucleic acid [fragment] to inhibit translation of [the] said viral nucleic acid sequence [containing an IRES] is detected by:

(a) contacting [the] said nucleic acid [fragment] with a reporter gene construct having the following elements [operatively] operably linked: a replication origin, a promoter, a reporter gene, and said IRES, under [the] conditions [sufficient to allow translation of the reporter gene to occur] where said reporter gene is translated;

(b) measuring the level of the translation product of [the] said reporter gene[-exposed to the nucleic acid fragment]; and

(c) comparing [the amount] said level of said translation product in (b) to the level of translation product synthesized by the reporter gene construct under the conditions of (a) but in the absence of said nucleic acid, thereby detecting said nucleic acid capable of inhibiting translation of said nucleic acid sequence [which was not exposed to the nucleic acid fragment, so that nucleic acid fragments which inhibit translation of nucleic acids containing said IRES are identified].

6. **(Canceled)** The method of claim 3 wherein said virus is selected from the group consisting of hepatitus A, and hepatitus C.

10. **(Once Amended)** The method of claim [3] 9, wherein said oligonucleotide further comprises a CAT nucleotide triplet.

17. **(Once Amended)** A pharmaceutical composition comprising a nucleic acid [fragment] encoding a sequence that is complementary to at least a portion of a [viral] Hepatitis A virus IRES which contains a Y[n]X[m] AUG sequence, and a pharmaceutically acceptable carrier, wherein the nucleic acid [fragment] is present in an amount effective for inhibiting viral replication, wherein Y is a pyrimidine tract between 4 to 12 nucleotides, and wherein X is a random spacer sequence of between 5 to 30 nucleotides.

18. **(Newly Added)** A composition comprising a nucleic acid encoding a sequence that is complementary to at least a portion of a Hepatitis A virus IRES which contains a YX AUG sequence, wherein the nucleic acid is present in an amount effective for inhibiting viral replication, and wherein Y is a pyrimidine tract between 4 to 12 nucleotides, wherein X is a random spacer sequence of between 5 to 30 nucleotides.